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THE EFFECTS OF DRUGS AND OTHER AGENCIES UPON THE RESPIRATORY MOVEMENTS.

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THE EFFECTS OF DRUGS AND OTHER AGENCIES UPON THE RESPIRATORY MOVEMENTS. By HORATIO C. WOOD, M.D., LL.D. (*Yale*), ASSISTED BY DAVID CERNA, M.D.

In physiological therapeutics a stimulant is a substance which increases functional activity. Accordingly, a vascular stimulant is one which increases the arterial pressure; or to speak more minutely, a cardiac or an arterial stimulant is one that increases the output of force by the heart or by the vaso-motor system. When, however, the function of respiration is in question, a stimulant, as the word is practically used by most pharmacologists, seems to be simply a substance which increases the rapidity of the respiration, since in almost all recorded experiments with drugs of the class, the experimentor has simply noted the rate of the respiration. Increased activity of rate does not however necessarily imply increased activity of the function. Thus, a rapid pulse may be a very feeble pulse, and an arterial sedative may increase the rate of the pulse though depressing most thoroughly the functional activity of the circulation. In like manner, it is shown by our experiments that very rapid breathing may coexist with very little movement of air. It is evident that the proper definition of a respiratory stimulant would be, that it is a substance which increases the amount of air taken in and out of the lungs in a fixed time.

Such considerations as these have led us to undertake the following research, which has for its object the determination of the respiratory movement of air as affected by different drugs and different agencies. The mode of research is in itself simple enough. It consists essentially of connecting the trachea of the animal with a tube which, in turn, is connected with two ordinary mercurial valves, the one of which allows the air to enter, the other the air to escape; the mercurial valve of expiration being, in turn, connected with an india-rubber bag or reservoir from which the air is drawn through by means of a suction-pump.

The rabbit would be an excellent animal for a research like the present, were not a certain amount of muscular force required to force the expired and inspired air through the mercurial valve. It is evident

that the muscular strength of the animal must be such that the very feeble resistance offered by the valves shall not be sufficient to embarrass respiration to the slightest extent. For this reason we have employed dogs. There are, however, two practical difficulties in the way of the experimentor, which can only be overcome by great care in estimating the results obtained by the experiments. The dog having practically no sweat gland, cools himself through forced respiration; further, in the dog, panting is the chief expression, not only of muscular and arterial excitement but also of purely nervous or emotional excitement. To illustrate the effect of excitement upon the respiration of the dog, we make one or two citations from our records of experiments.

Exp. I. A dog weighing 9 kilos, in a state of great emotional excitement, was found to be moving 0·32 cubic foot of air per minute; twenty minutes afterwards, however, when he had become quiet, he only passed through his lungs 0·05 foot per minute. In another experiment (Exp. II.) a dog weighing about 10 kilos, when quiet passed 0·14 cubic foot per minute; fifteen minutes later, when he had been only moderately excited, he passed 0·27 cubic foot per minute.

There is scarcely any stimulant which by a direct action upon the respiratory centres is capable of so exciting respiration in the dog as is emotion; so that in order to get the normal standard with which the effects of the remedy may be compared, it is essential that the experimentor wait until the animal has become calm. In order also to make even the results thus obtained positive, it seems essential to check them by experiments made when the animal is rendered unconscious, and therefore incapable of emotional excitement, by chloral or other drugs, even though these drugs be distinct respiratory depressants.

In estimating the effect of a respiratory depressant, such as chloral, it is plain that the calming influence of the drug must be allowed for, as possibly having immense influence. In this case, also, the physiologist must check his first results by noting the effects of repetitions of the dose of the chloral or other sedative remedy after unconsciousness has been reached; it being plain that in a true respiratory sedative a repeated dose should cause repeated fall of respiration, although the first dose had produced unconsciousness.

As the dog protects itself from high external heat through the respiration, it is to be expected that heat is in the dog a powerful and direct respiratory stimulant. In endeavouring to experimentally test the truth of this *a priori* reasoning, we placed the body of the dog in a

double metallic box, so arranged that the animal lay comfortably in his trough, not in contact anywhere with the metallic surface, with the head out of the box, and the mouth and breathing apparatus connected with the air of the room; we then filled the double metallic box with hot water. In this way, as much as possible, we avoided producing pain or excitement, or interfering with the respiration or the supply of fresh air to the animal. As illustrating the effect produced we briefly outline two experiments. (Exp. III.), a dog, weight not noted, with a rectal temperature of 39·2 C., breathing at the rate of 20 a minute, moving in the same period 0·14 foot per minute, was surrounded with water at 73° C. Five minutes afterwards the respiratory rate had risen to 42, and the air moved to 0·23 foot per minute; fifteen minutes after this, the rectal temperature of the dog was 40·8 C., the respiratory rate 58, and the air moved 0·3 foot per minute. The animal having been lifted out of the box, in fifteen minutes the rectal temperature had fallen to 39·8 C., the respiration to 22, the air moved to 0·16 foot. The animal was replaced in the box, in 15 minutes the rectal temperature had risen to 40·9 C., the respiration to 82, the air moved to 0·42 foot per minute. Again taken out of the box, in half-an-hour the rectal temperature had dropped to 39·3 C., respiratory rate to 18, the air moved to 0·1 foot per minute.

In a second experiment, the air movement in a very small dog was 0·06 per minute, the rectal temperature being 39·3 C., and the temperature of the air 60 F.; when under the influence of a box temperature of 70 C., the rectal temperature had been raised to 40·3 C., the air movement was increased to 0·12. A little later, when the rectal temperature was 42·5, the air movement was 0·25. It is worthy of being put on record, as one of the phenomena of over-heating or thermic fever in the dog, that by-and-by the air movement lessens. Thus, five minutes before the animal just spoken of died from the over-heating, the air movement was 0·16, the rectal temperature being 43 C.

In a number of experiments, which it is not necessary to further detail, we have obtained concordant results, and have proven that in the dog heat is a most powerful stimulant to the respiratory centres. Any clinician who has noted the effect of fever in increasing the respiratory rate in man, must, it seems to us, recognize that as in the dog so also in the man is heat a powerful respiratory stimulant; the difference in the man and the dog in this respect being in degree rather than in kind.

Sometime since, Dr Lauder Brunton called attention to the great importance of maintaining the bodily temperature in narcotic poisoning, and showed that in the dog the fatal effects of otherwise lethal doses of narcotics might be set aside by placing the animal in heated chambers. Our experiments naturally suggest that as in narcotic poisoning the animal usually dies of respiratory paralysis, the antagonistic effect of the heat is due to its stimulating respiratory centres. In order to test this explanation, we have made two experiments, one with morphine and one with chloral, which we append.

EXPERIMENT IV.

Period	Rect. temp.	Movement of air cu. ft.	Resp. rate	Remarks
	C.			
1	38·5	0·16	42	Weight 7·7 kilos.
2				Given 12 grs. morphine into jugular in divided dose.
3	37·2	0·15		Complete narcotism; paraplegia. Dog now put in hot box, and kept there, getting abundant air for respiration.
4	39·3	0·38	94	Dog returned to box.
5	39·5	0·37	100	

EXPERIMENT V.

1	38	0·16	21	Weight 5·5 kilos. Given 3 grs. chloral.
2	37·5	0·13	18	Dog given 5 more grs. chloral.
3		0·12	22	Complete unconsciousness. 3 grs. more chloral given.
4				Dog was now put into hot box. Rectal temperature, through a misunderstanding, not taken.
5		0·27	100	Dog taken out; afterwards replaced.
6	40	0·67	90	Dog taken out of box and allowed to stay out.

An examination of the records just given will show the enormous effect of heat upon the respiration in narcotism. The first dog was completely narcotized (its spinal cord indeed being almost completely paralyzed) by 12 grains of morphia. During the narcotism the rectal temperature had fallen 1·03 C. below the norm. When by means of external heat the rectal temperature was raised about one degree above the norm, the respiratory rate was more than doubled, and the movement of air in the chest increased from 0·15 cubic foot per minute, to 0·38 cubic foot.

In the second experiment, a small dog was completely narcotized by 11 grains of chloral, with pronounced fall in the rectal temperature and the reduction of air movement per minute from 0·16 cubic foot to 0·12 cubic foot, but when by means of the hot box the rectal temperature of the animal was put up two degrees above the norm, the air movement rose to nearly five times the normal amount.

These experiments demonstrate that the stimulating effect of heat upon the respiratory centres is as great in the narcotized as in the normal animal. They also explain the way in which heat protracts or even saves life during narcotism, and enforce the necessity—by means of the hot water bath or bed—of overheating the human body when respiratory paralysis from the action of some narcotic agent is threatened.

Before attempting the experimental study of the influence of individual drugs upon the amount of air taken in and expelled from the lungs, we made a series of experiments to determine the effect of section of the pneumogastric upon the respiratory movement of air. The only experiments upon this subject with which we are acquainted are those of Rosenthal, who states that the amount of air inspired in a given time by the rabbit is not affected by section of the pneumogastric, although in doves the amount is diminished. Our own experiments upon the dog not under the influence of any drug are five in number.

Experiment VI.

Time min.	Rate of resp.	Cubic feet movement of air per min.	Remarks
0		1·0	Weight of dog 18 kilos. Dog somewhat excited.
10	40	0·68	Dog quiet.
15		1·7	Vagi were now cut.
24		3·5	
40	60	3·0	
60	80	3·1	

Experiment VII.

0	69	0·3	Weight of dog 10 kilos.
10			Par vagum cut.
12	43	0·47	
25	21	0·3	
35	84	0·43	Breathing very irregular.

EXPERIMENT VIII.

Time min.	Rate of resp.	Cubic feet movement of air per min.	Remarks
0	36	0·7	Weight of dog 15 kilos. Dog very quiet.
5			Par vagum cut.
17	12	0·35	
30	9	0·48	Dog very quiet.

EXPERIMENT IX.

Time min.	Rate of resp.	Cubic feet movement of air per min.	Remarks
0	66	0·44	Weight of dog 9·7 kilos.
10			Par vagum cut. Next period 15 mins. after section.
28	18	0·28	
43	18	0·24	Dog very quiet.

EXPERIMENT X.

Time min.	Rate of resp.	Cubic feet movement of air per min.	Remarks
0	69	0·39	Dog not struggling.
10			Par vagum cut.
12	33 to 53	0·46	Dog struggling part of time.
20	18 to 24	0·24	Dog quiet.
30	24 to 108	0·36	Much of the time respiration very short and rapid.

On examination these records will show that in Exp. VI. the section of the vagi was followed by a great rise both in the number of respirations and in the amount of air expired; the last period at which the experiment was studied being forty-five minutes after the section of the vagus. In Exp. VII., although the respiration fell finally to less than one-third of what it had been before section of the vagi, there was no sensible reduction in the amount of air expired; indeed, during a portion of the time, with lessened respiratory rate, there was pronounced increase of air movement. Later in the experiment, nearly half-an-hour after section of the vagi, for reasons not very evident, the rate increased and the movement of the air was greater than before the section. In Exp. VIII. both rate and air movement were distinctly lessened after the section of the vagi, the rate falling from one-third to one-fourth of what it had been previous to the section, and the air movement being but a little over one-half what it had been before section. In Exp. IX., again there was a decrease both in rate and in amount of air moved, the rate falling to a little over one-quarter, the movement of air to a little over one-half of what it had been before the section. In Exp. X., the respiratory rate fell directly after the section of the vagi, but the amount of air moved increased. Some minutes later, with the respiratory rate

about one-third what it was before section, the movement of air was reduced about one-third; after this again the respiration increased in frequency to at least the norm, and the inspired air also became practically the same as before the section.

These experiments show that the action of section of the vagi upon air movements in the dog varies; that usually, when the rate falls and the ordinary slow full breathing of pneumogastric section is obtained, the total amount of air moved is less than the norm; on the other hand, in some cases after section of the par vagum, the gain in the extent of the respiratory movements more than compensates for the loss in rate.

It is also plain that the influence of section of the vagi upon the respiratory movements may be in the dog dominated by general or emotional excitement, disturbances of temperature, etc. All our experiments were made with the dog kept at a uniform temperature, so as to put aside this source of error. Every effort was also made to keep the dog as quiet as possible, and the following experiment was also instituted, in which by the benumbing influences of chloral, disturbing influences should be shut out from the respiratory centre.

EXPERIMENT XI.

Time min.	Drug chloral 5 °/₀ sol.	Cubic feet movement of air per min.	Rate of resp.	Remarks
0		1·0	129	Weight 20 kilos.
5 to 20	25 c.c.			
22		0·68	60	Completely chloralized.
25				Par vagum divided.
28		0·5	114	
38		0·3	58	

In this experiment the usual effect of chloral in reducing the respiratory rate and the movement of air was obtained. Under these circumstances section of the vagus was followed by an increase of the respiratory rate, which increase soon, however, in great part subsided. Even during the period of increased rate the movement of air was less after than before the cutting of the nerve, and when the rate a little later fell to near what it had been before section the movement of air became less than half what it had been before section.

These experiments, when taken together, seem to us to warrant the conclusion that in the dog the general tendency is towards a lessened movement of air after section of the vagi, but that this tendency is not

sufficiently strong to prevent its being set aside by disturbing causes: and that sometimes after section of the pneumogastrics the respiratory movement of air is not only not lessened but is increased without our being able to assign a reason for the exceptional results.

Respiratory Depressants.

Chloral.

The first drug which we studied was chloral. We have already given one or two experiments with this drug, and add in tabular form five more.

Exp.	Before chloral		Chloral injected 10 % sol.	After chloral		Remarks
	Cubic feet movement of air normal	Resp. rate		Movement of air during anæsth.	Resp. rate	
XII.	0·22	54	5 c.c.	0·11	30	Weight 6·8 kilos.
XIII.	0·27	56	5 c.c. 5 c.c.	0·24 0·14	72 58	Weight 8·2 kilos.
XIV.	0·4	74	20 c.c. 5 c.c.	0·19 0·14	54 34	Weight 12·7 kilos.
XV.	0·22	64	10 c.c.	0·1	31	Weight 7 kilos.
XVI.	0·15	35	10 c.c. 10 c.c.	0·12 0·9	32 30	

A study of the above table will show that in all the experiments the reduction in the amount of inspired air produced by complete chloralization is very pronounced. In many cases the decrease of respiratory air movement amounts to fifty per cent., and sometimes even to seventy-five per cent. The results which we have obtained by the use of chloral are concordant, and demonstrate that in the dog chloral is a true respiratory depressant, markedly reducing the respiratory movement of air.

The action of chloral upon man is evidently similar to that which it exerts upon the dog, and the conclusion which has been reached in our experiments is applicable to human beings.

Morphine.

The next drug which we studied is morphine. We give in the following table six experiments with the drug.

EXPERIMENT XVII.

Time min.	Morphine sulph. injected jugular 5 % sol.	Movement of air cubic ft.	Resp. rate	Remarks
0		0·17	70	Weight of dog 12 kilos.
5	10 c.c.			Respiration at once arrested. Artificial resp. resorted to; after a few minutes, natural breathing.
18		0·07	17	
28		0·11	25	

EXPERIMENT XVIII.

Time min.	Morphine sulph. injected jugular 5 % sol.	Movement of air cubic ft.	Resp. rate	Remarks
0		0·08	13	Weight 15·5 kilos.
5	5 c.c.			Breathing stopped entirely. Artificial respiration resorted to.
15		0·08	12	
22	5 c.c.			
25		0·05	12	
32	5 c.c.			
37		0·05	12	
40	5 c.c.			
46		0·1	12	
54	5 c.c.			
59		0·06	11	
63	10 c.c.			
68		0·10	12	Respirations very deep. Coma.
72	15 c.c.			
75		0·08	12	Reflexes increased.

EXPERIMENT XIX.

Time min.	Morphine sulph. injected jugular 5 % sol.	Movement of air cubic ft.	Resp. rate	Remarks
0		0·11	36	Weight 7·5 kilos.
5	1·5 c.c.			
9		0·04	13	
12	1·5 c.c.			
16		0·09	40	
20	3 c.c.			
25		0·052	12	
32		0·052	12	Complete anæsthesia.
40	3 c.c.			
45		0·048	14	
49	3 c.c.			
54		0·048	14	
58	6 c.c.			
63		0·1	20	Violent jerking or convulsive movements. Cheyne-Stokes respiration.
68		0·06		

EXPERIMENT XX.

Time min.	Morphine sulph. injected jugular 5 % sol.	Movement of air cubic ft.	Resp. rate	Remarks
0		0·12	42	Weight 7·7 kilos.
5	2·5 c.c.			Breathing stopped. Artificial resp. for 3 minutes.
17		0·06	24	
20		0·056	24	
22	1·25 c.c.			
28		0·07	21	

EXPERIMENT XXI.

0		0·31	42	Weight 19·5 kilos.
5		0·27	42	
6	5 c.c.			
10		0·04	10	
15		0·1	15	

In almost all our experiments with morphine we found that the first injection of the drug into the jugular vein, even if the quantity employed were not very large, produced an immediate arrest of respiration so severe and so permanent, that in order to save the animal artificial respiration had to be resorted to. After this first injection enormous amounts of the alkaloid were tolerated with comparatively light effect. Immediately after recovery from the first injection, the respiratory movement of the air was usually greatly reduced, but if the experiment were continued respiration often recovered itself, and though enormous amounts of the drug had been employed and coma produced, the air movement often finally became almost or altogether equal to the norm. Thus in Exp. XVIII., a dog weighing 15½ kilos took 50 c.c. of a 5 % solution of morphine, which is equal to 2½ grammes or about 37 grains of the alkaloid; yet at the end of the experiment the air movement as well as the rate of respiration were practically what they had been in the beginning. In Exp. XIX., a dog weighing 7·5 kilos took 18 c.c. without distinct change in the air movement.

In all these experiments in which, after a very large dose of morphine, the increase took place in the respiratory movements, the reflexes were markedly increased, and often violent convulsive movements present. As it is well known, morphine has in the lower animals

a marked stimulating influence upon the spinal cord; and as in our experiments, the increase of the respiratory movement of air late in the morphine poisoning was always associated with distinct evidences of spinal excitement, it is probable that the increased respiration was dependent upon or connected with this spinal excitement.

The detailed explanation of the action of morphine upon the respiratory function in the dog still remaining uncertain, it is very difficult, if not impossible, to apply the results which have been obtained with dogs to the study of the action of the drug upon the respiratory function in man.

Respiratory Stimulants.

The drugs which are commonly reputed to be respiratory stimulants, whose action upon the movement of air we have studied, are atropine, strychnine, and cocaine.

In our experiments with these alkaloids, we have been careful to see that the temperature of the animal and its surroundings was kept uniform; and in order to avoid any fallacy which might arise from the emotional or other excitement produced by the drug, increasing the respiratory movement, we have made with each drug three sets of experiments; first, upon the normal animal: second, upon the animal partially narcotized with morphine: third, upon the animal completely chloralized.

As has already been shown, the action of morphine upon the respiratory function of the dog is so peculiar that at present much importance cannot be attached to experiments made with a supposed respiratory stimulant on a dog narcotized with an opiate. On the other hand, the chloralized dog is not only entirely freed from the disturbing influence of emotion, but is also under the influence of a consistent and persistent respiratory depressant; and any drug which is a true respiratory stimulant ought to demonstrate its activity upon the chloralized animal.

Atropine.

We have made four experiments upon the normal dog with the sulphate of atropine, using always the one and a half per cent. solution injected into the jugular vein. These experiments are as follows:

EXPERIMENT XXII.

Time min.	Atropine 1–2 % solution	Movement of air cubic ft.	Resp. rate	Remarks
0		0·09	19	Dog extremely fat and sluggish ; weight 32 kilos.
5		0·1	12	
10	5 c.c.			
18		0·31	43	Five mins. after injection dog breathing convulsively; otherwise quiet.
25		0·17	23	Dog very quiet.
37	5 c.c.			
43		0·4	104	Breathing irregular in rate.
53		0·22	34	
55	5 c.c			
61		0·36	72	
73		0·16	24	
75	10 c.c.			
83		0·18	48	Dog, when let out, able to walk staggeringly.

EXPERIMENT XXIII.

Time min.	Atropine 1–2 % solution	Movement of air cubic ft.	Resp. rate	Remarks
0		0·22	136	Dog, weight 26 kilos.
5	10 c.c.			
12		0·36	125	
18		0·48	110	
30		0·42	52	
31	10 c.c.			
43		0·22	48	
50		0·22	27	
52	10 c.c.			
55		0·1	16	Dog died directly after last observation.

EXPERIMENT XXIV.

Time min.	Atropine 1–2 % solution	Movement of air cubic ft.	Resp. rate	Remarks
0		0·05	11	Dog, weight 10 kilos.
5	10 c.c.			
12		0·08	27	
15	10 c.c.			
20		0·14	33	
35		0·09	21	
37	10 c.c.			
42		0·12	20	
52		0·12	24	

EXPERIMENT XXV.

Time min.	Atropine 1–2 % solution	Movement of air cubic ft.	Resp. rate	Remarks
0		0·25	81	Weight 10·2 kilos.
5	5 c.c.			
11		0·32	154	
16		0·34	150	
23		0·46	162	
25	5 c.c.			
29		0·40	180	
35		0·36	180	
38	10 c.c.			
44		0·34	180	
49		0·29		
52	10 c.c.			
58		0·34	156	
63		0·37		
65	10 c.c.			
70		0·33	140	
72	10 c.c.			
76		0·26	78	
82		0·34	180	Dog had long been perfectly quiet and paralyzed.
88	20 c.c.			
93		0·09	88	Dog killed.

The first effect of the atropine is to enormously excite the respiratory function; this primary excitement is soon followed, unless the dose of atropine have been very great, by a distinct fall in the air movement, which fall, however, is not sufficient to overcome the first rise, so that the air movements remain for a long time distinctly above the norm. Thus, in Exp. XXII., 5 c.c. increased in eight minutes the air movement from 0·1 to 0·31, but seven minutes later the movement was 0·17, which figure was increased by a second injection of 5 c.c. to 0·4, followed in ten minutes by a fall to 0·22. In this experiment the dog was a very large one, weighing 32 kilos, and although altogether 25 c.c. of the atropine solution were given, the air movement at the end was nearly double what it was in the beginning.

An examination of Exp. XXIV. will show that the results were completely parallel to those just discussed. In Exp. XXV., the final result of repeated injections amounting in all to 70 c.c. was to reduce

the air movements much below the norm. In Exp. XXIII. the dog was watched until just before death from the atropine, and in this case also, after a period of great increase in the air movement, a gradual reduction took place: nevertheless, it is somewhat remarkable that the movements of the air continued so large almost up to death; the amount being 0·1 per minute just before the animal ceased to live.

In regard to the amount of increase attained by atropine, in the first experiment the increase was 300 %; in the second, 100 %; in the third, 100 %; and in the fourth not quite 100 %.

The experiments which we have made with Morphine and Atropine are as follows:

EXPERIMENT XXVI.

Time min.	Atropine 1 % solution	Movement of air cubic ft.	Resp. rate	Remarks
0		0·1	25	Animal under influence of 10 c.c. of 1 % solution of morphine. Weight 12 kilos.
5	5 c.c.			
10		0·1	25	
12	5 c.c.			
18		0·06	20	
20	5 c.c.			
27		0·06	15	

EXPERIMENT XXVII.

0		0·072	24	Air movement been reduced by 5 c.c. of 5 % sol. of morphine from 0·12. Weight 7 kilos.
5	1 c.c.			
10		0·068		Profound anæsthesia.
13	1 c.c.			
16		0·056	24	
21	2 c.c.			
25		0·068	24	
29		0·078	18	
35	2 c.c.			
40		0·058	18	
44	3 c.c.			
50		0·068	30	Killed.

EXPERIMENT XXVIII.

Time min.	Drug	Movement of air cubic ft.	Resp. rate	Remarks
0		0·065		Dog normal. Weight 10 kilos.
	30 c.c. atropine 1 %			
20		0·12	22	
24	5 c.c. morphine 1 %			
32		0·032	14	

In looking over these experiments it will be noted that in Exp. XXVI. and XXVII. the atropine failed entirely to increase the respiratory movements of air in the dog under the influence of opium; indeed there seemed to be a distinct decrease in the air movement after the exhibition of the atropine. In Exp. XXVIII. a dog 10 kilos in weight, whose air movements had been nearly doubled by the exhibition of 30 c.c. of a one per cent. solution of atropine, was given 5 c.c. of the one per cent. solution of morphine, the result being a fall of nearly seventy-five per cent. in the air movements.

The results of these experiments are rather surprising, and are difficult of explanation. It is possible, however, that the doses of morphia were too large for their influence to be overcome by atropine. At any rate, before any positive conclusions can be fairly drawn, further experimentation seems essential.

The experiments with chloral and atropine are as follows:

Experiment XXIX.

Time min.	5 % sol. chloral, 1 % sol. atropine	Movement of air cubic ft.	Resp. rate	Remarks
0	30 c.c. chloral	0·15		Weight 8·9 kilos.
20		0·08	30	
25	5 c.c. atropine			
28		0·2		Cheyne-Stokes breathing, with violent rapid breathing in paroxysms, then quiet slow breathing.
33		0·2		
36	3 c.c. atropine			
42		0·18		Breathing as before.
45	15 c.c. chloral			
48		0·1		Some evidence still of Cheyne-Stokes, but paroxysms very slight.
55	10 c.c. chloral			
66		0·096		

Experiment XXX.

0		0·12	22	Dog, weight 18·3 kilos: had taken before record 13 c.c. chloral solution.
5	10 c.c. atropine			
10		0·22	32	
15		0·19		
20	5 c.c. atropine			
23		0·36	92	
28	5 c.c. atropine			
32		0·34	88	
36	5 c.c. atropine			
40		0·24	44	

In these experiments the results are concordant. We were able in chloralized dogs, by the use of atropine, to increase the air movement 250 per cent. In Exp. XXIX. it was found possible, by a re-injection of chloral, to reduce for a second time the air movement; the antagonism between the respiratory actions of the chloral and atropine being very plain.

These experiments show that both in the normal and in the chloralized dog, the salts of atropine greatly increase the respiratory movement of air, and lead to the conclusion that atropine is a direct and powerful stimulant to the respiratory function.

The experiments which we have made with strychnine upon the normal animal are as follows:

EXPERIMENT XXXI.

Time min.	Strychnine grammes	Air movement cubic ft.	Resp. rate	Remarks
0		0·05	95	Weight 9 kilos.
3	0·0002			
12	0·0004			
19		0·11	74	Dog quiet, but has spasms when touched.
27		0·06		
42	0·0004			
50		0·06	30	Pronounced spasms.
56		0·11	33	Dog very quiet.

EXPERIMENT XXXII.

0		0·14	54	Weight 9·9 kilos.
10	0·0005			
20		0·31		Died three minutes later.

EXPERIMENT XXXIII.

0		0·1		Weight 9·9 kilos.
5–15	0·0007			
25		0·46		Dog quiet.
33		0·21		

EXPERIMENT XXXIV.

0		0·09	30	Weight 8 kilos
2	0·0005			
14		0·1	25	
23		0·09	24	
26	0·0005			
33		0·14	28	Reflexes abnormally active.
42		0·12	24	
46	0·0005			
51		0·154	27	Slight spasms.
60		0·36	94	Dog quiet.
70		0·262	88	

Experiment XXXV.

Time min.	Strychnine grammes	Air movement cubic ft.	Resp. rate	Remarks
0		0·5		Weight 9 kilos.
5	0·0002			
9		0·6		
10	0·0004			
15		0·85		Distinct reflex tremors.

Experiment XXXVI.

0		0·14		Weight 10 kilos.
5	0·007			
10		0·27		
15		0·31		Dog died shortly after last, in spasms.

Experiment XXXVII.

0		0·16		Weight 10 kilos.
5	0·00045			
15		0·19		
18	0·0007			
25		0·36		

Experiment XXXVIII.

0		0·12		Weight 8 kilos.
3	0·00075			
7		0·13		
10	0·00076			
15		0·26		

An examination of the table given above will show that the results are concordant, and that the injection of strychnine produces an extraordinary increase in the respiratory air movement; the increase in Exp. XXXI. amounting to over 100 per cent.: in Exp. XXXII. to over 100 per cent.: in Exp. XXXIII. to over 250 per cent.: in Exp. XXXIV. to 300 per cent.: in Exp. XXXV. to 75 per cent.: and in Exps. XXXVI., XXXVII., and XXXVIII., to considerably over 100 per cent.

With Morphine and Strychnine we have performed a single experiment, Exp. XXXIX. (see over).

The record in this will show that under the influence of the strychnine there was an increase in the air respiratory movement of 60 %, which increase was afterwards almost completely overcome by a re-injection of the solution of morphine.

EXPERIMENT XXXIX.

Time min.	5 % sol. morphine, 1–4 % sol. strychnine	Movement of air cubic ft.	Resp. rate	Remarks
0		0·1	15	Weight 19·5 kilos. Reduced by 5 c.c. 5 % solution of morphine from 0·27.
5	0·75 c.c. strychnine			
15		0·16	15	Convulsive startings.
18		0·15	24	
25	8 c.c. morphine			
30		0·16		Convulsive twitchings still.
40	3 c.c. morphine			
43		0·15	12	Convulsive movements still.
50	5 c.c. morphine			
55		0·11	15	

The experiments upon chloralized animals are as follows:

EXPERIMENT XL.

Time min.	Chloral. 5 % sol. strychnine. grammes	Movement of air. cubic ft.	Resp. rate	Remarks
0		0·22	54	Weight 6·8 kilos.
0–20	15 c.c. chloral			
25		0·122	30	Animal chloralized.
28	0·0003 strychnine			
35		0·138	45	
48		0·174	48	
51	5 c.c. chloral			
60		0·108	36	
63	0·0003 strychnine			
72		0·146	46	
82		0·15	57	
84	0·0002 strychnine			Immediately slight spasms.
94		0·184	48	
101		0·144		Slight spasms.
103	0·0002 strychnine			Immediately death in spasms.

EXPERIMENT XLI.

Time min.	Chloral. 5 % sol. strychnine. grammes	Movement of air. cubic ft.	Resp. rate	Remarks
0		0·27	56	Weight 8·2 kilos.
0–17	20 c.c. chloral			
35		0·142	60	
36	0·0008 strychnine			
45		0·228	79	
47	0·0005 strychnine			
54		0·26	87	
55		0·292	72	
57	0·0005 strychnine			
65		0·261	72	Dog killed.

EXPERIMENT XLII.

Time min.	Chloral. 5 % sol. strychnine. grammes	Movement of air. cubic ft.	Resp. rate	Remarks
0		0·39	74	Weight 12·7 kilos.
0–20	25 c.c. chloral			
35		0·14	34	
36	0·0005 strychnine			Complete anæsthesia.
43		0·536	82	Dog quiet.
44	10 c.c. chloral			
52		0·154	35	
55	0·0005 strychnine			
61		0·236	62	
62	0·0005 strychnine			
65		0·34	78	Eye reflexes return.
68	15 c.c. chloral			
74		0·126	36	Reflexes gone.

EXPERIMENT XLIII.

Time min.	Chloral. 5 % sol. strychnine. grammes	Movement of air. cubic ft.	Resp. rate	Remarks
0		0·276	60	Weight 7·5 kilos.
0–60	40 c.c.			
75		0·114	32	
85		0·138		
86	0·001 strychnine			
96		0·13	34	
98	0·001 strychnine			
108		0·26	38	
116		0·26	51	

The results in the above experiments are concordant. In Exp. XL., the respiratory air movement, which had fallen to forty per cent. under chloral, was restored nearly to the norm. In Exp. XLI., after a similar fall under chloral, the respiratory air movement was increased distinctly beyond the norm. In Exp. XLII., before the chloral the air movement was 0·39, after the chloral it was 0·14, and was increased by the strychnine to 0·536. In Exp. XLIII., before the chloral the air movement was 0·276, after the chloral it fell to 0·114, but was practically restored to the norm by the strychnine.

The experiments which we have made with strychnine upon normal and narcotized animals, are all in accord in showing that the alkaloid powerfully influences the respiratory movement of air, and that it is therefore a true respiratory stimulant.

Cocaine.

The experiments made with cocaine upon the normal animal are as follows:

Experiment XLIV.

Time min.	1 % sol. cocaine	Movement of air. cubic ft.	Resp. rate	Remarks
0		0·254	20	Weight 11·3 kilos.
5	3 c.c.			
15		0·48	24	
19	5 c.c.			
25		0·402	24	
35		0·54	110	
40		0·66	125	Animal restless; very excited. Killed.

Experiment XLV.

0		0·186	22	Weight 10·5 kilos.
5	5 c.c.			
12		0·28	28	
15	5 c.c.			
30		0·42	40	
40		0·65	90	
52		0·64	112	
67		0·714	140	Killed.

EXPERIMENT XLVI.

Time min.	1 % sol. cocaine	Movement of air. cubic ft.	Resp. rate	Remarks
0		0·072	18	Weight 5·2 kilos. Very quiet.
2	3 c.c.			
10		0·108	21	
12	3 c.c.			
16		0·11	19	
19	5 c.c.			Violent tetanoid convulsions.
23		0·098	20	
28		0·072	15	Very quiet.
30	3 c.c.			
34		0·062	21	Very quiet.
36	4 c.c.			
40		0·25	36	Violent convulsions.
43	3 c.c.			Died directly after last dose.

The above experiments are all concordant in showing that cocaine in the normal animal enormously increases the amount of air movement; the increase being usually greatest when the tetanoid convulsive movements produced by toxic doses of cocaine are marked. Under these circumstances the increase may amount to two to three hundred per cent.

The only experiments which we have made with cocaine upon the narcotized animal are as follows:

EXPERIMENT XLVII.

Time min.	5 % sol. chloral 1 % sol. cocaine	Movement of air. cubic ft.	Resp. rate	Remarks
0–30	45 c.c. chloral			Weight 11·3 kilos.
35		0·272	120	Corneal reflex very slight.
40	8 c.c. cocaine			
45		0·164	42	
50	10 c.c. cocaine			
55		0·184	60	
58	5 c.c. cocaine			
63		0·22		
67	5 c.c. cocaine			
		0·17	48	

Experiment XLVIII.

Time min.	5 °/₀ sol. chloral, 1 °/₀ sol. cocaine	Movement of air. cubic ft.	Resp. rate	Remarks
0–20	20 c.c. chloral			Weight about 10 kilos.
24		0·14	23	
25	6 c.c. coc.			
31		0·14	26	
34		0·2	33	Very restless.
41		0·22	24	
50		0·16	22	
52	4 c.c. coc.			
57		0·22	33	
62		0·22	30	
65	4 c.c. coc.			Violent tetanoid convulsions at once.
72		0·26	36	

An examination of the above records will show that Exp. XLVIII. in which the animal had received nearly 20 c.c. of the 5 °/₀ solution of chloral per kilo, the cocaine very distinctly affected the respiratory air movement, in fact nearly doubling it; whilst in Exp. XLVII., in which the animal received 45 c.c. per kilo, cocaine was powerless to increase the air movement, which steadily and persistently fell under the continuing influence of the chloral.

The conclusions which are deducible from the experiments which we have made with cocaine, are: that it acts as a powerful respiratory stimulant, whose influence, however, fails in the presence of an overwhelming dose of a respiratory depressant.

Comparative Value of the Respiratory Stimulants.

The experiments which we have made prove that the three alkaloids, atropine, strychnine, and cocaine, are all respiratory stimulants, increasing the amount of air taken in and out of the lungs; exerting action, apparently, by a direct influence upon the nerve-centres which preside over the respiratory movements. The question which of these alkaloids is the most powerful and reliable in practical medicine, can scarcely be answered positively by means of experimentation upon the lower animals. It has, however, seemed worth while to make a comparative study, as throwing some light upon the practical value of the remedies.

In the first series of experiments we took three dogs, as nearly alike in weight and other characteristics as possible, and injected into the jugular vein of each of them 2 c.c. per kilo, of the 5 °/₀ solution of chloral,

and then tested the effect of cocaine, atropine, and strychnine, upon the respiratory air movements. In the second series of experiments 3 c.c. of the chloral solution per kilo of weight were administered.

Experiments upon dogs which had received 2 c.c. per kilo of a 5 °/₀ solution of Chloral.

EXPERIMENT XLIX.

Time min.	Drug	Movement of air. cubic ft.	Resp. rate	Remarks
0		0·07	28	Weight 6·1 kilos. Reflexes gone.
5	3 c.c. 4 °/₀ sol. cocaine			Immediate violent tetanoid convulsions; finally cramps, asphyxia; artificial resp. kept up a minute, restored to life.
12		0·14	46	Still convulsions.
17		0·12	33	Still convulsions.
27		0·08	24	
28	2 c.c. 1 °/₀ sol. atropine			
33		0·09	26	
36	2 c.c. 1 °/₀ sol. atropine			
40		0·13	30	
43	2 c.c. 1 °/₀ sol. atropine			
47		0·12	37	
50	2 c.c. 1 °/₀ sol. atropine			
54		0·14		

EXPERIMENT L.

Time min.	Drug	Movement of air. cubic ft.	Resp. rate	Remarks
0		0·16	90	Weight 5·9 kilos. Very quiet. Reflexes very weak.
3	3 c.c. 1 °/₀ sol. atropine			
7		0·15	54	
12	7 c.c. 1 °/₀ sol. atropine			
17		0·14		
22		0·14	45	

EXPERIMENT LI.

Time min.	Drug	Movement of air. cubic ft.	Resp. rate	Remarks
0		0·066	24	Weight 5·8 kilos.
7	0·12 c.c. 1 % sol. strychnine			
12		0·092	18	
22		0·098	24	Dog killed.

Experiment upon dogs which had received 3 c.c. per kilo of a 5 % solution of Chloral.

EXPERIMENT LII.

Time min.	Drug	Movement of air. cubic ft.	Resp. rate	Remarks
0		0·37	140	Weight 18 kilos.
5	3 c.c. 1 % sol. cocaine			Dog ceased breathing directly after injection. Artificial respiration required to bring him to.
10		0·24	28	
25		0·29	28	
27	2 c.c. 1 % sol. cocaine			
30		0·39	44	Dog struggling.
35		0·52	48	
42		0·53	104	

EXPERIMENT LIII.

0		0·25	50	Weight 22 kilos.
5	5 c.c. 1 % sol. atropine			
9		0·46	85	
15		0·39	102	
20	5 c.c. 1 % sol. atropine			
26		0·45	70	
35		0·52	96	
41	10 c.c. 1 % sol. atropine			
49		0·43	114	

EXPERIMENT LIV.

Time min.	Drug	Movement of air. cubic ft.	Resp. rate	Remarks
0		0·25	128	Weight 15·8 kilos.
5	0·1 c.c. 1 % sol. strychnine			
10		0·31	160	
17		0·39	180	
20	0·4 c.c. 1 % sol. strychnine			
26		0·33	196	
30	0·2 c.c. 1 % sol. strychnine			
35		0·34	168	Tetanic spasms.
45				Dog died of strychnine poisoning.

An examination of the results which we have tabulated will show that the cocaine doubled the air movement after the 2 c.c. of chloral per kilo, and increased the air movement nearly fifty per cent. after the 3 c.c. The atropine did not increase the air movement after the 2 c.c. of chloral materially, but more than doubled the air movement after the 3 c.c.; whilst the strychnine increased the air movement to fifty per cent. after the 2 c.c., and also after the 3 c.c. of chloral solution.

In endeavouring to formulate from these six experiments a conclusion as to the comparative value of the three respiratory stimulants, an almost insuperable difficulty appears in the lack of uniformity of result. We can assign no reason why the atropine failed in the one case and acted so extraordinarily in the other. This irregularity or inequality of action, however, is paralleled in the experiments with atropine which we recorded earlier in this paper; since the atropine failed to increase the respiratory air movement in every experiment which we made upon the dog narcotized with morphia.

The influence of the cocaine as a respiratory stimulant has throughout our research been found very pronounced, and in these recent experiments its influence was even more marked than that of strychnine. Cocaine, however, in Exp. XLVII. did not increase in the chloralized dog the movement of air. On the other hand, in no experiment with strychnine have we failed to obtain a result, and we think, therefore, whilst,

at times and perhaps usually, the influence upon the respiratory air movement of atropine and of cocaine is greater than that of strychnine, yet strychnine is more positive and certain in asserting its influence in the face of powerful respiratory depressant drugs than are the other alkaloids.

Although the conclusions which we have reached have been based solely upon the results of experiments made upon dogs, we think they are in accord with results obtained by clinicians in the treatment of disease, and that they apply to the man as well as to the dog. The difficulty with the use of massive doses of cocaine and strychnine in practical medicine is the danger that attends their action on other portions of the nervous centres than the respiratory tract, and atropine, though probably not the most certain and powerful, seems the safest drug of the three, when it has been determined to get to the fullest possible influence of the agent used. We would call attention, however, to the fact that in Exp. XLIX., after cocaine had been given to the point of producing convulsions, and the first excitement of the respiratory movement had somewhat subsided, atropine exerted a pronounced influence in increasing respiration; and we believe that the best results can be obtained in practical medicine, by the simultaneous use of two or more of the respiratory stimulants. Cocaine and strychnine have so much similarity of action upon the nerve-centres that the use of one will probably increase any danger that may have been incurred by the administration of large doses of the other. The relations of atropine to cocaine and strychnine, however, are different, and it would seem that by the consentaneous use of atropine and strychnine, or of atropine and cocaine, may be obtained the advantages of what has been denominated by Dr H. C. Wood in his *Treatise on Therapeutics*, as "crossed action;" the two drugs touching and reinforcing one another in their influence upon the respiratory functions, and spreading wide apart from each other in their unwished for and deleterious actions.

UNIVERSITY OF PENNSYLVANIA,
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